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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,499	10/28/2003	Vincenzo Scarlato	2300-0363.01	7930

27476 7590 10/19/2006

NOVARTIS VACCINES AND DIAGNOSTICS INC.
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EXAMINER	
GRASER, JENNIFER E	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,499	SCARLATO ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,8,10-13 and 18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2 and 3* is/are allowed.

6)☒ Claim(s) *8,10-13 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/302,626.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted on 9/1/06 is made. Claims 2, 3, 8, 10-13 and 18-21 are currently pending.

little as one nucleotide.

Claim Rejections - 35 USC § 112-Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 8, 10-13 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "an isolated nucleic acid sequence comprising SEQ ID NO:3', ' an isolated nucleic acid sequence which encodes a protein comprising the amino acid sequence set forth in SEQ ID NO:4', and isolated nucleic acid molecules which hybridize to these nucleic acid molecule under high stringency conditions (provided they are specifically recited in the claim and the function that said nucleic acid can detect N.meningitidis DNA through hybridization), does not reasonably provide enablement for isolated nucleic acid sequences fully complementary to a nucleic acid which encode a polypeptide 50% or greater identity to an isolated amino acid sequence of SEQ ID NO:4, an isolated nucleic acid molecule comprising a nucleotide sequence encoding *any* immunogenic polypeptide, wherein the nucleotide sequence has 50% or greater identity to a nucleic acid sequence of SEQ ID No:3,

isolated nucleic acid sequences which encode 10-mer fragments or isolated nucleic acid sequences which encode immunogenic polypeptides which have amino acid sequences which are 80-95% identical to SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the instant claims is drawn to polynucleotides which are not specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what nucleic acids may be changed without causing a detrimental effect to the adhesion and penetration protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. To start with the DNA sequence first, this requires even more work on the part of the skilled artisan.

The instant claims are drawn to nucleic acids comprising a sequence with a given percent similarity to a nucleic acid which encodes a protein. Selective point mutation to one key residue could eliminate the function of the polypeptide. It could

eliminate its adhesion and penetration properties. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. As stated above, Applicants have not shown which nucleotides may be changed without causing a detrimental effect to the protein in which it encodes. The claims allow for as great as 50% variation. This is a huge variation allowing for many gaps, insertions, substitutions and deletions. It is unclear that a sequence with this much variation would even have the ability to detect *N.meningitidis* in a hybridization assay. Applicants have provided no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different

biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. The specification also fails to teach the location of immunogenic epitopes. Therefore, it would take undue experimentation for one of skill in the art to determine which 30 nucleotides would encode a 10-mer immunogenic fragment. Given the lack of guidance contained in the specification regarding acceptable nucleotide substitutions, additions or deletions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicants' Arguments:

Applicants argue that the claimed compound or composition is limited by a particular use and the claims should be evaluated based upon that limitation. Applicants argue that the specification on page 45, line 18 through page 46, line 6 discusses use of Neisserial antigens in immunodiagnostic assays for detecting antibody levels and such Neisserial antigens may be expressed using nucleotide sequences as claimed. This argument has been fully and carefully considered, but is not commensurate in scope with the claimed invention. The instant claims allow for DNA encoding 'any immunogenic polypeptide with as little as 50% identity to SEQ ID NO:4". These peptides may not have the ability to detect N.meningitidis, much less any Neisseria bacterium. Further, the claims do not require the polypeptides to have the

ability to bind to an amino acid sequence comprising SEQ ID NO:4. Additionally, the specification fails to provide and enable nucleic acid sequences which could encode such variant sequences. To start with the DNA sequence first, this requires even more work on the part of the skilled artisan. The instant claims recite only a very generic use, e.g., encode an immunogenic polypeptide. This generic scope does not require the polypeptides to specifically bind to an amino acid sequence comprising SEQ ID NO:4 and ultimately detect N.meningitidis. Further, it would take a great deal of experimentation on the part of the skilled artisan to begin with the nucleic acid as claimed and work to find acceptable variants which would express the polypeptides having this ability. It is suggested, if written support is provided in the instant claims, that the variants be drawn to sequences which hybridize under specific conditions to SEQ ID NO:3 and can detect N.meningitidis DNA.

The instant claims are drawn to variants which differ by 50% from the known sequences. This is a very large amount. It is unclear that sequences differing by this much would have the ability to successfully detect N.meningitidis. Additionally, it is unclear how to produce and identify variants which would produce an immunogenic polypeptide with this much variation from the sequences which are taught. This is a huge variation allowing for many gaps, insertions, substitutions and deletions. It is even more unlikely that such variants would produce a functional protein or immunogenic fragment. As stated above, Applicants have provided no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be

made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. Further, it would take undue experimentation for one of skill in the art to determine which 30 nucleotides would encode a 10-mer immunogenic fragment, particularly when no immunogenic epitopes have been identified. Given the lack of guidance contained in the specification regarding acceptable nucleotide substitutions, additions or deletions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation. It is suggested that Applicants limit the claims to molecules displaying greater homology, e.g., 90-95% homology, and which are capable of detecting N.meningitidis DNA through hybridization in order to overcome the rejection.

Claim Rejections - 35 USC § 112-Written Description

4. Claims 8, 10-13 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO: 3 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated nucleic acid sequence consisting of SEQ ID NO: 3 and equivalent degenerative codon sequences thereof, but not the full breadth of the claims, meets the written description provisions of 35 USC 112, first paragraph.

5. Claims 2 and 3 are allowed.

6. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Navarro, can be reached on (571) 272-0861.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser
Primary Examiner
Art Unit 1645

10/6/06